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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LI, QIAN JANICE	
ART UNIT	PAPER NUMBER
1633	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/659,034	SHIZUYA, HIROAKI	
	Examiner	Art Unit	
	Q. JANICE LI, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/25/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-14,16,17,25,27-40,45 and 46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-14, 16, 17, 25, 27-40, 45, 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/24/08 has been entered.

Claims 1, 11, 25, 45 have been amended. Claims 2, 15, 18-24, 26, 41-44, 47-52 have been canceled. Claims 1, 3-14, 16, 17, 25, 27-40, 45, 46 are pending and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-14, 16, 17, 25, 27-40, 45, 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because of the claim recitation "thereby *allowing for modification* of [the] human DNA of the ligated chimeric DNA constructs". It is unclear why ligating the human DNA ends of the first and second chimeric DNA constructs would allow the modification and thus the meaning of the phrase is unclear in the context of the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-5, 8-11, 13, 16, 17, 25, 27-29, 32-35, 37, 39, 40, 45, 46 are rejected under 35 U.S.C. 103(a) as being obvious over *Shiao et al.* (Transgenic Res 1999;8:295-302), in view of *Akiyama et al.* (Nucleic Acids Res 2000;28(e77):i-vi).

Shiao teaches a method of making a humanized transgenic mouse whose genome comprising a gene replacement construct comprising a human glucagon receptor (GR) gene flanked by a first and second mouse DNA sequence orthologous to and have the same order and orientation relative to human DNA sequence. *Shiao* teaches the design of the GR replacement vector to include the murine 5' flanking region fused with the entire human GR gene at the common start condon site so that the expression of the human GR gene was under the control of the mouse promoter and expressed in a tissue specific manner (column 2, page 298). *Shiao* goes on to

teach to include the 3' flanking sequence from the mouse GR gene to promote efficient targeting (allows for homologous recombination).

Shiao differs from instant claims in that the gene replacement vector was not generated by generating and ligating two chimeric vectors as instantly claimed, and the targeting/replacement vector was not a bacterial artificial chromosome (BAC).

Akiyama supplemented the deficiency by establishing it was known in the art to use a ligation method for efficiently inserting selection markers to a target gene for selection of a recombinant event. *Akiyama* discloses a method comprising the steps of digesting a bacterial artificial chromosome (BAC) vector containing a target gene at a site within the target gene (=generating chimeric vectors), inserting a selection marker cassette, and then ligating the ends of the split target gene, and the vector was ready (=the third construct, a BAC) for introducing into ES cells. Figure 2 of *Akiyama* is a schematic drawing of the steps and the homologous recombination between the genomic target and the replacement targeting vector, step e shows a linearized BAC vector. *Akiyama* teaches this method is simple and rapid for constructing gene targeting/replacement vectors, requires only small amount of sequence information, and can be applied to many organisms (e.g. the abstract). *Akiyama* also teaches introducing the vector into mouse ES cells for recombination as an example.

Although *Akiyama* does not teach inserting the selection marker cassette into an intron of the target gene, it would have been common knowledge in the art to do so to avoid disruption of a gene product when the vector was used for replacement as taught by *Shiao*.

Accordingly, it would have been obvious to the skilled in the art to apply the method taught by *Akiyama* for inserting a selection marker in the targeting vector as taught by *Shiao* and using a BAC vector for carrying large amount of genomic sequence with a reasonable expectation of success. The skilled in the art would have been motivated to do so because it improves efficiency for inserting a selection marker in a targeting/replacement vector. Accordingly, the claimed invention as a whole was *prima facie* obvious in the absence of sufficient, clear and convincing evidence to the contrary.

Claims 1, 3-5, 8-11, 13, 16, 17, 25, 27-29, 32-35, 37, 39, 40, 45, 46 are rejected under 35 U.S.C. 103(a) as being obvious over *Divoky et al.* (Proc. Natl. Acad. Sci. USA 98(3): 986-991, 30 Jan. 2001), in view of *Akiyama et al.* (Nucleic Acids Res 2000;28(e77):i-vi).

Divoky discloses a gene replacement construct for performing homologous recombination in a mouse ES cell, and a transgenic mouse made from the ES cell. The initial mouse genomic sequence is carried by a bacterial artificial chromosome (BAC, e.g. column 2, page 986). The construct comprises the coding region of the human erythropoietin receptor gene (EPOR) from the start codon to the stop codon flanked by first and second mouse genomic DNA sequences. The first mouse DNA sequence is approximately 7 kb of genomic sequence upstream from the start codon of the mouse EPOR gene, and the second mouse DNA sequence is approximately 5 kb downstream from the stop codon of the mouse EPOR gene, i.e. the portion of the mouse EPOR gene from the start to stop codons has been replaced with its human ortholog. The

human EPOR coding sequence comprises a positive selection marker expression cassette (*flox-neo*), inserted within an intron. The DAN construct was used to replace the mouse EPOR coding sequence in one copy of the EPOR gene in a mouse ES cell. These ES cells were then implanted into mouse blastocysts, which were implanted into a pseudopregnant mouse to produce a chimeric "humanized" mouse which was then bred to produce transgenic humanized mice carrying one or two copies of the human EPOR coding sequence in place of the orthologous mouse EPOR coding sequence. See page 986, col. 2, through page 987, col. 1; page 987, col. 2; Fig. 1, page 988).

Divoky differs from instant claims in that the replacement vector was not generated by generating and ligating two chimeric vectors as instantly claimed and the final vector was not a bacterial artificial chromosome (BAC).

Akiyama supplemented the deficiency by establishing it was known in the art to use a ligation method for inserting selection markers to a target gene for selection of a recombinant event. *Akiyama* discloses a method comprising the steps of digesting a bacterial artificial chromosome vector containing a target gene at a site within the target gene (=generating chimeric vectors), inserting a selection marker cassette, and then ligating the ends of the split target gene, and the vector was ready (=the third construct, a BAC) for introducing into ES cells. Figure 2 of *Akiyama* is a schematic drawing of the steps and the homologous recombination between the genomic target and the replacement targeting vector, step (e) shows a linearized BAC vector. *Akiyama* teaches this method is simple and rapid for constructing gene targeting/replacement vectors, requires only small amount of sequence information, and can be applied to many

organisms (e.g. the abstract). *Akiyama* also teaches introducing the vector into mouse ES cells as an example.

Accordingly, it would have been obvious to the skilled in the art to apply the method taught by *Akiyama* for inserting a selection marker in the targeting vector as taught by *Divoky* using a BAC vector for carrying large amount of genomic sequence with a reasonable expectation of success. The skilled in the art would have been motivated to do so because it improves efficiency for constructing a replacement vector. Accordingly, the claimed invention as a whole was at least *prima facie* obvious in the absence of sufficient, clear and convincing evidence to the contrary.

Claims 12, 14, 36, 38 are rejected under 35 U.S.C. 103(a) as being obvious over *Divoky et al.* (Proc. Natl. Acad. Sci. USA 98(3): 986-991, 30 Jan. 2001), in view of *Akiyama et al.* (Nucleic Acids Res 2000;28(e77):i-vi) as applied to claims 1, 3-5, 8-11, 13, 16, 17, 25, 27-29, 32-35, 37, 39, 40, 45, 46 above, further in view of *Tzimagiorgis et al.* (Nucleic Acids Res. 1996;24:3476-7)

The teaching of *Divoky* in view of *Akiyama* does not teach adding a selection marker following the recombining step or a selection marker flanking the first and second DNA sequences.

Tzimagiorgis supplemented the deficiency. *Tzimagiorgis* teaches a single step ligation method for introducing a selection marker into a replacement vector at the ends (flanking the first and second DNA sequences) of a replacement vector in order to avoid laborious cloning procedures. *Tzimagiorgis* concluded this fast and simple method

consistently provides a high level of enrichment of appropriately targeted clones containing the replacement vector (e.g. the abstract).

Accordingly, it would have been obvious to the skilled in the art to apply the method taught by *Tzimagiorgis* for inserting a selection marker flanking the first and second DNA sequences in a gene replacement vector as taught by *Divoky* in view of *Akiyama,* and using a BAC vector for carrying large amount of genomic sequence with a reasonable expectation of success. The skilled in the art would have been motivated to do so because it improves efficiency for inserting markers in a targeting/replacement vector. Accordingly, the claimed invention as a whole was at least *prima facie* obvious in the absence of sufficient, clear and convincing evidence to the contrary.

Claims 6, 7, 30, 31 are rejected under 35 U.S.C. 103(a) are rejected under 35 U.S.C. 103(a) as being obvious over *Divoky et al.* (Proc. Natl. Acad. Sci. USA 98(3): 986-991, 30 Jan. 2001), in view of *Akiyama et al.* (Nucleic Acids Res 2000;28(e77):i-vi) as applied to claims 1, 3-5, 8-11, 13, 14, 16, 17, 25, 27, 32, 34, 35, 37, 39, 40, 45 above, and further in view of *Heintz et al* (Nat Rev 2001;2:861-70).

The teaching of the *Divoky* in view of *Akiyama* differs from instant claims in that they did not use *E coli* for the recombining process or explicitly teach the reasoning for using a BAC construct.

Heintz supplemented the deficiency by establishing that at the time of instant filing date, that BAC has become the choice of vehicles for genome analysis, and making targeting vectors to generate transgenic mouse. Compared to other

conventional vectors such as YACs, BACs are simple to prepare and manipulate, can carry several hundred kilobases of DNA, propagated at low copy number, and more stable (e.g. box 1). *Heintz* teaches the use of reporter genes and targeted-expression have been crucial in the analysis of gene expression and function in many studies including making transgenic animals, but limited in mammalian studies by the intrinsic difficulty of identifying key regulatory elements and large genome manipulation. *Heintz* teaches the F-factor-based bacterial artificial chromosomes provide a tool that took advantage of the precision of homologous recombination in recombination-deficient strain of *E. coli* (such as a recA mutation, claim 7), which had been used extensively for marker insertion into, and excision from the bacterial genome (e.g. box 1). *Heintz* reviews technical aspects regarding how the BAC works for making target vectors by homologous recombination in the recombination-deficient strain of *E. coli*: a) restoring the capability of homologouse recombination of the BAC by the reintroduction of the *E. coli recA* gene, for example; b) targeting the desired modification cassette into a precise site on the genomic DNA insert using a shuttle vector that carries the desired reporter gene or modification cassette, flanked by sequences homologous to the genomic DNA carried in the BAC; c). using positive and negative selection markers to select correct recombination, to enrich the desired end-product, i.e. a BAC that carries the modification cassette inserted into the exact position chosen in the design of the experiment (e.g. column 1, page 862). *Heintz* goes on to teach multiple recombination steps might be necessary for resolution or excision. *Heintz* also teaches the BAC

system has been successfully used to insert reporter genes into large segment of CNS-expressed genes and BAC transgenic mice have been made (column 2, page 862).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method taught by *Heintz et al.,* for making the targeting vector as taught by *Divoky et al.* in view of *Akiyama et al.* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the advantage of the BAC system as taught by *Heintz et al.* Given the success in the art for making BAC transgenic mouse, one would have had a reasonable expectation of success for inserting any human/animal gene of interest into a mouse genome. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. JANICE LI, M.D.** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9 AM -7:00pm, Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is **(866) 217-9197**. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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/Q. JANICE LI, M.D./
Primary Examiner, Art Unit 1633